Genetic removal of matrix metalloproteinase 9 rescues the symptoms of fragile x syndrome in a mouse model.

Journal: J Neurosci

Publication Year: 2014

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PubMed link: 25057190

Funding Grants: ES-Derived Cells for the Treatment of Alzheimer's Disease

Public Summary:
Fragile X syndrome (FXS) is the largest known single gene cause of autism, affecting approximately 1 in 4000 male births. Features can include obsessive compulsive behaviors, repetitive behaviors, cognitive deficits, and susceptibility to noise-induced seizures. FXS patients also show characteristic physical traits that include, long faces, large ears, loose joints, soft and fragile skin and enlarged testis in males. FXS is caused by mutation in the FMR1 gene on the X chromosome, which is why the majority of FXS subjects are male. In previous reports we established that synaptic and behavioral abnormalities associated with FXS could be ameliorated in the mouse model by a drug (minocycline) that inhibits the activation and activity of an extracellular enzyme called MMP-9. In this paper we describe how the loss of MMP-9 gene products eliminate behavioral and physical traits of FXS in the mouse model. This reports provides compelling evidence that autistic behaviors and other features of FXS are caused by too much MMP-9 activity. As MMP-9 is a normal protein expressed the brains of all people, this study may have implications for autism research for FXS patients and perhaps others on the autistic spectrum.

Scientific Abstract:
Fmr1 knock-out (ko) mice display key features of fragile X syndrome (FXS), including delayed dendritic spine maturation and FXS-associated behaviors, such as poor socialization, obsessive-compulsive behavior, and hyperactivity. Here we provide conclusive evidence that matrix metalloproteinase-9 (MMP-9) is necessary to the development of FXS-associated defects in Fmr1 ko mice. Genetic disruption of Mmp-9 rescued key aspects of Fmr1 deficiency, including dendritic spine abnormalities, abnormal mGluR5-dependent LTD, as well as aberrant behaviors in open field and social novelty tests. Remarkably, MMP-9 deficiency also corrected non-neural features of Fmr1 deficiency-specifically macroorchidism-indicating that MMP-9 dysregulation contributes to FXS-associated abnormalities outside the CNS. Further, MMP-9 deficiency suppressed elevations of Akt, mammalian target of rapamycin, and eukaryotic translation initiation factor 4E phosphorylation seen in Fmr1 ko mice, which are also associated with other autistic spectrum disorders. These findings establish that MMP-9 is critical to the mechanisms responsible for neural and non-neural aspects of the FXS phenotype.